

# PATENT ABSTRACTS OF JAPAN

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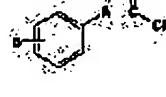
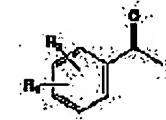
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## (54) NEW HYDROXAMIC ACID DERIVATIVE

### (57) Abstract:

**PROBLEM TO BE SOLVED:** To provide the subject new compound having differentiating-inducing action of cancer cell and useful as a medicine for treatment, improvement, etc., of malignant tumor, autoimmune diseases and skin diseases.

**SOLUTION:** This compound is represented by formula I [A is CH<sub>2</sub>CH<sub>2</sub>, CH=CH or C≡C; B is a group, etc., of formula II to formula V (R<sub>1</sub> and R<sub>2</sub> are H, amino, nitro, hydroxyl, a halogen, a 1-4C alkyl, a 1-4C alkoxy, etc.) and B is bound to meta position or para position to the component A], e.g. 3-[4-(N,N-dimethyl)amino]benzoylcinnamohydroxamic acid. The compound of formula I is obtained by subjecting, e.g. a compound represented by formula VI to condensation reaction (conventional amide bond forming reaction in peptide, e.g. method of an active ester or mixed acid anhydride in an organic solvent, at -20 to 50°C for 0.5-48hr) with a compound of the formula, H<sub>2</sub>N-OH.



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**LEGAL STATUS**

[Date of request for examination]

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JAPANESE [JP,10-182583,A]

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CLAIMS DETAILED DESCRIPTION TECHNICAL FIELD PRIOR ART EFFECT OF THE  
INVENTION TECHNICAL PROBLEM MEANS EXAMPLE

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[Translation done.]

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## \* NOTICES \*

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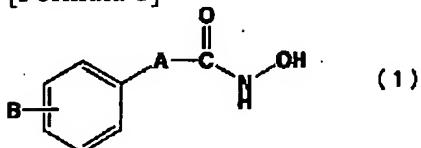
1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. \*\*\*\* shows the word which can not be translated.
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## CLAIMS

[Claim(s)]

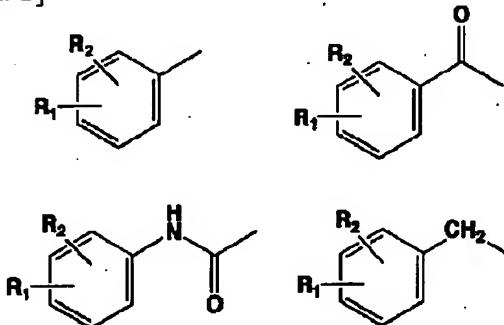
[Claim 1] a general formula -- (1 [-izing 1])

[Formula 1]



A expresses a -CH<sub>2</sub>-CH<sub>2</sub>-radical, a -CH=CH-radical, or a -C\*\*C-radical among [type. B expresses either of the account [ degree ] structures [-izing 2].

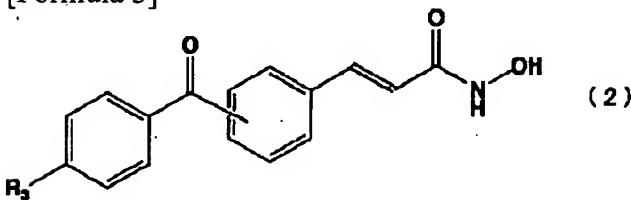
[Formula 2]



(R1 and R2 express independently a hydrogen atom, the amino group, a nitro group, hydroxyl, a halogen atom, the alkyl group of carbon numbers 1-4, the alkoxy group of carbon numbers 1-4, the alkylamino radical of carbon numbers 1-4, the dialkylamino radical of carbon numbers 1-4, or the alkylthio group of carbon numbers 1-4 among a formula, respectively.) However, B is combined with the meta position or the para position to A.] The hydroxamic acid derivative come out of and expressed, and its salt permitted in pharmacology.

[Claim 2] Formula 2 [-izing 3]

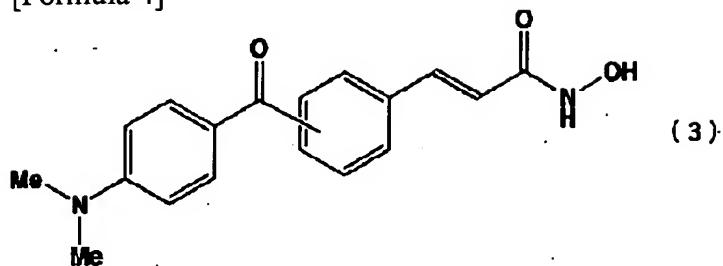
[Formula 3]



[-- R3 expresses a hydrogen atom or a dimethylamino radical among a formula, and permutation benzoyl is combined with the meta position or the para position to a -CH=CH-radical.] The hydroxamic acid derivative according to claim 1 come out of and expressed, and its salt permitted in pharmacology.

[Claim 3] Formula 3 [-izing 4]

[Formula 4]



[-- permutation benzoyl is combined with the meta position or the para position to a -CH=CH-radical among a formula.] The hydroxamic acid derivative according to claim 1 come out of and expressed, and its salt permitted in pharmacology.

[Claim 4] Drugs which contain a compound according to claim 1 to 3 as an active principle.

[Claim 5] The anticancer agent which contains a compound according to claim 1 to 3 as an active principle.

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[Translation done.]

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**DETAILED DESCRIPTION**

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**[Detailed Description of the Invention]****[0001]**

[Industrial Application] This invention relates to a new hydroxamic acid derivative. It is related with use in the anticancer agent and drugs based on a differentiation-inducing operation of a new hydroxamic acid derivative in more detail.

**[0002]**

[Description of the Prior Art] By the time the death by current and cancer extracts death by the heart disease and the cerebrovascular disease and occupies a primacy in a cause of death, it will have become. On the other hand, research of various cures, such as a surgical operation, radiotherapy, a thermotherapy, and a chemotherapy, has so far been done for ascendancy of cancer. Although a chemotherapy is one of the big columns of cancer treatment and many drugs have been found out especially until now, though regrettable, the present condition is drugs' satisfying enough not being found out but waiting eagerly for new drugs, also including a side effect till today.

[0003] Many anticancer agents found out so far used the cancer cell itself as the target, and have been chosen for the purpose of killing all the cells that became cancer. It was what demonstrates the carcinostatic effectiveness by carrying out a direct action to DNA in a cancer cell, and making the killer cell effectiveness discover as the device. However, these anticancer agents were lacking in the selectivity of a cancer cell and a normal cell, and the side effect discovered in a normal cell as a result became a limitation on a therapy in many cases.

[0004] On the other hand, the differentiaion inducer aims at controlling the property (reproductive integrity) which the cancer cell instead of the direct killer cell effectiveness has, and urging differentiation to a cancer cell also in the anticancer agent. Since various check devices act on the cell which specialized and it is led to a natural death of a cell, finally it may happen to growth control of a cancer cell, and the regression of cancer. Although it is not the anticancer agent which has the killer cell effectiveness in respect of the regression of cancer because of the mechanism of a differentiation-inducing operation, selectivity with a normal cell, low toxicity, etc. are expectable by one side. [by which it is known well that the retinoic acid which is a differentiaion inducer is actually used for a therapy, and high effectiveness is shown by the myelogenous leukemia before acute -- Huang et al. --;Blood, 72,567-572 (1988), Castaign et al. --;Blood, and 76 and 1704 --] besides -1709 (1990) or Warrell;New Engl.J.Med., 324, and 1385-1393 (1991).

[0005] Moreover, since a vitamin D derivative shows a differentiation-inducing operation, many application to an anticancer agent is also studied [others [ 5867 / Olsson;Cancer Res., 43, and / (1983) / 5862-]]. In response to these researches, the application to anticancer agents, such as the vitamin D derivative (JP,6-179622,A) which is a differentiaion inducer, an isoprene derivative (JP,6-192073,A), a tocopherol (JP,6-256181,A), a quinone derivative (JP,6-305955,A), an un-annular poly isoprenoid (JP,6-316520,A), a benzoic-acid derivative (JP,7-206765,A), and a glycolipid (JP,7-258100,A), is reported. However, there are no drugs which reached sufficient level on cancer treatment, to various kinds of cancers, it is effective and drugs with high safety are strongly desired by these researches.

[0006]

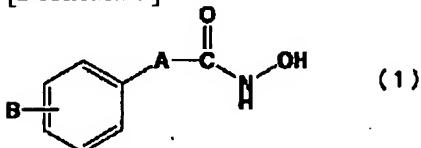
[Problem(s) to be Solved by the Invention] The technical problem of this invention has a differentiation-inducing operation of a cancer cell, and is to offer a compound useful as drugs, such as a malignant tumor, an autoimmune disease, and therapy / improvement medicine of a dermatosis.

[0007]

[Means for Solving the Problem] As a result of inquiring wholeheartedly that the above-mentioned technical problem should be solved, this invention persons found out that a new hydroxamic acid derivative had a differentiation-inducing operation, and completed this invention. That is, this invention is [0008]. [1] a general formula -- (1) [-izing 5]

[0009]

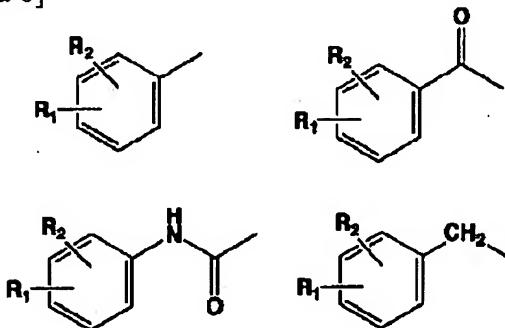
[Formula 5]



A expresses a -CH<sub>2</sub>-CH<sub>2</sub>-radical, a -CH=CH-radical, or a -C\*\*C-radical among [type. B expresses either of the account [ degree ] structures [-izing 6].

[0010]

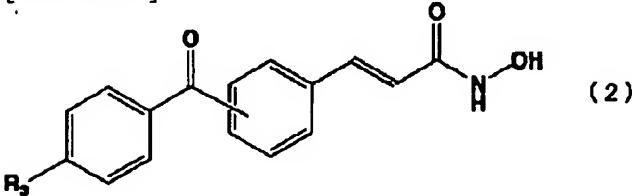
[Formula 6]



(R1 and R2 express independently a hydrogen atom, the amino group, a nitro group, hydroxyl, a halogen atom, the alkyl group of carbon numbers 1-4, the alkoxy group of carbon numbers 1-4, the alkylamino radical of carbon numbers 1-4, the dialkylamino radical of carbon numbers 1-4, and the alkylthio group of carbon numbers 1-4 among a formula, respectively.) However, B is combined with the meta position or the para position to A.] It is the hydroxamic acid derivative come out of and expressed, and its salt permitted in pharmacology, and is [0011]. [2] Formula 2 [-izing 7]

[0012]

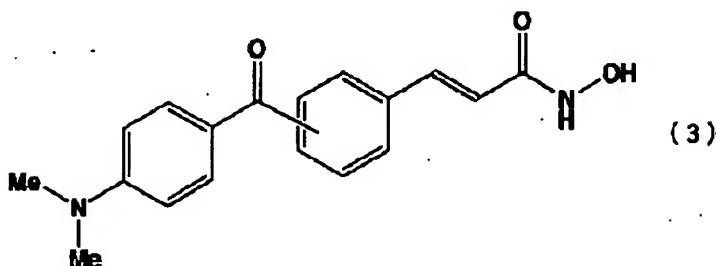
[Formula 7]



[-- R3 expresses a hydrogen atom or a dimethylamino radical among a formula, and permutation benzoyl is combined with the meta position or the para position to a -CH=CH-radical.] It is the hydroxamic acid derivative given in [1] come out of and expressed, and its salt permitted in pharmacology, and is [0013]. [3] Formula 3 [-izing 8]

[0014]

[Formula 8]



[-- permutation benzoyl is combined with the meta position or the para position to a -CH=CH-radical among a formula.] It is the hydroxamic acid derivative given in [1] come out of and expressed, and its salt permitted in pharmacology, and is [0015]. [4] [1] It is the drugs which contain the compound of a publication as an active principle in either of - [3], and is [0016]. [5] [1] It is the anticancer agent which contains the compound of a publication as an active principle in either of - [3].

[0017]

[Embodiment of the Invention] Hereafter, this invention is explained to a detail.

[0018] The carbon number per unit substituent is expressed in the carbon numbers 1-4 as used in the field of this invention. That is, in the case of a dialkyl permutation, carbon numbers 2-8 are meant. With a halogen atom, a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom can be mentioned.

[0019] With the alkyl group of carbon numbers 1-4, a methyl group, an ethyl group, n-propyl group, an iso-propyl group, n-butyl, iso-butyl, sec-butyl, t-butyl, etc. can be mentioned.

[0020] With the alkoxy group of carbon numbers 1-4, a methoxy group, an ethoxy radical, n-propoxy group, an iso-propoxy group, an allyloxy radical, an n-butoxy radical, an iso-butoxy radical, a sec-butoxy radical, a t-butoxy radical, etc. can be mentioned. With the alkylamino radical of carbon numbers 1-4, for example, N-methylamino radical, N-ethylamino radical, a N-iso-propylamino radical, a N-n-propylamino radical, a N-n-butylamino radical, etc. can be mentioned.

[0021] With the dialkylamino radical of carbon numbers 1-4, also when an alkyl group is the same It is contained also when it differs. For example, N and N-dimethylamino radical, N, and N-diethylamino radical, With the alkylthio group of the carbon numbers 1-4 which can mention an N-ethyl-N-methylamino radical, an N-methyl-N-n-propylamino radical, an N-ethyl-N-n-propylamino radical, etc., a methylthio radical, an ethyl thio radical, n-propyl thio radical, etc. can be mentioned.

[0022] With the salt of the compound permitted pharmacologically, a salt with inorganic bases, such as organic bases, such as alkaline earth metals, such as alkali metal, such as a lithium, sodium, and a potassium, magnesium, and calcium, monomethylamine, ethylamine, dimethylamine, a trimethylamine, triethylamine, and benzylamine, and ammonia, can be mentioned.

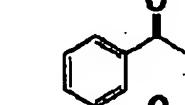
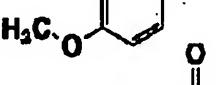
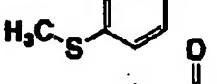
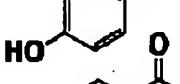
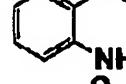
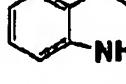
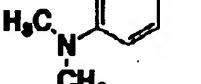
[0023] When the compound of a formula (1) has basicity, such as an amino group, an alkylamino radical, and a dialkylamino radical, a salt with organic acids, such as an acetic acid besides inorganic acids, such as a hydrochloric acid regularly used in this field, a hydrobromic acid, a sulfuric acid, and phosphoric acid, a tartaric acid, a fumaric acid, a maleic acid, a citric acid, a benzoic acid, trifluoroacetic acid, and p-toluenesulfonic acid, can also be mentioned as a salt of a compound. With drugs, therapy / improvement medicine, such as an anticancer agent or an autoimmune disease, and a dermatosis, can be mentioned.

[0024] It is containing one or more compounds expressed with a general formula (1) that it contains as an active principle in pharmaceutical preparation.

[0025] When the compound of a general formula (1) has asymmetrical carbon, these contain the racemic modification and each optically active substance of all.

[0026] Hereafter, the representation compound expressed with the general formula (1) of this invention is concretely illustrated to Table -1 [the table 1-table 9]. In addition, this invention is not limited to these examples.

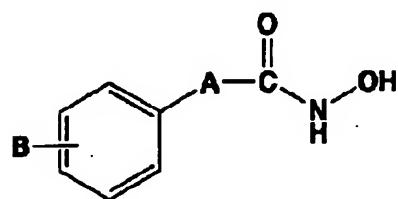
[0027]

化合物番号	B	Bの置換位置	A
1		m	
2		m	
3		m	
4		m	
5		m	
6		m	
7		m	
8		p	
9		p	
10		p	

[Table 1] Table -1

[0028]

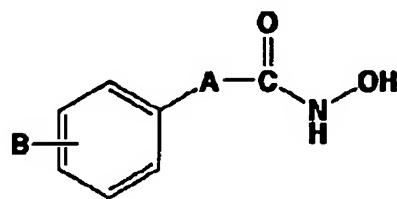
[Table 2] 1 of a Table -1 continuation



化合物番号	B	Bの置換位置	A
11		m	
12		m	
13		m	
14		m	
15		m	
16		m	
17		m	
18		p	
19		p	
20		p	

[0029]

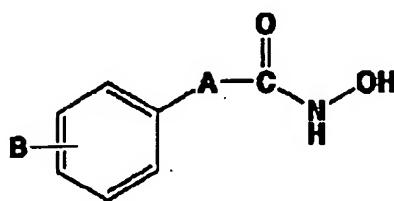
[Table 3] 2 of a Table -1 continuation



化合物番号	B	B の置換位置	A
21		m	
22		m	
23		m	
24		m	
25		m	
26		m	
27		m	
28		p	
29		p	
30		p	

[0030]

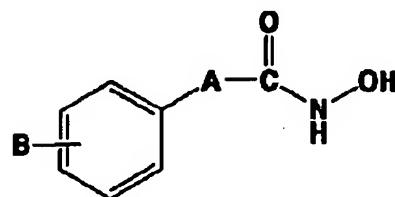
[Table 4] 3 of a Table -1 continuation



化合物番号	B	B の置換位置	A
31		m	
32		m	
33		m	
34		m	
35		m	
36		m	
37		m	
38		p	
39		p	
40		p	

[0031]

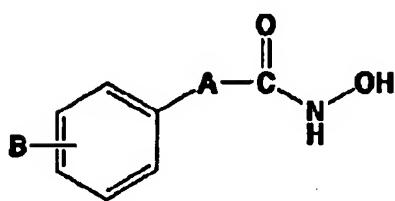
[Table 5] 4 of a Table -1 continuation



化合物番号	B	Bの置換位置	A
41		m	-CH <sub>2</sub> CH <sub>2</sub> -
42		m	-CH <sub>2</sub> CH <sub>2</sub> -
43		m	-CH <sub>2</sub> CH <sub>2</sub> -
44		m	-CH <sub>2</sub> CH <sub>2</sub> -
45		m	-CH <sub>2</sub> CH <sub>2</sub> -
46		m	-CH <sub>2</sub> CH <sub>2</sub> -
47		m	-CH <sub>2</sub> CH <sub>2</sub> -
48		p	-CH <sub>2</sub> CH <sub>2</sub> -
49		p	-CH <sub>2</sub> CH <sub>2</sub> -
50		p	-CH <sub>2</sub> CH <sub>2</sub> -

[0032]

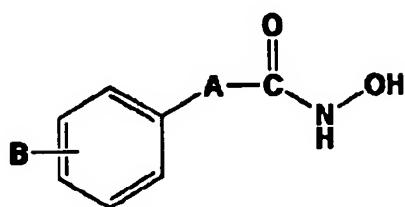
[Table 6] 5 of a Table -1 continuation



化合物番号	B	Bの置換位置	A
51		m	-CH <sub>2</sub> CH <sub>2</sub> -
52		m	-CH <sub>2</sub> CH <sub>2</sub> -
53		m	-CH <sub>2</sub> CH <sub>2</sub> -
54		m	-CH <sub>2</sub> CH <sub>2</sub> -
55		m	-CH <sub>2</sub> CH <sub>2</sub> -
56		m	-CH <sub>2</sub> CH <sub>2</sub> -
57		m	-CH <sub>2</sub> CH <sub>2</sub> -
58		p	-CH <sub>2</sub> CH <sub>2</sub> -
59		p	-CH <sub>2</sub> CH <sub>2</sub> -
60		p	-CH <sub>2</sub> CH <sub>2</sub> -

[0033]

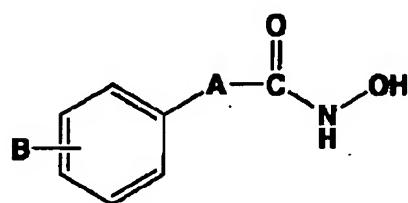
[Table 7] 6 of a Table -1 continuation



化合物番号	B	Bの置換位置	A
61		m	-C≡C-
62		m	-C≡C-
63		m	-C≡C-
64		m	-C≡C-
65		m	-C≡C-
66		m	-C≡C-
67		m	-C≡C-
68		p	-C≡C-
69		p	
70		m	

[0034]

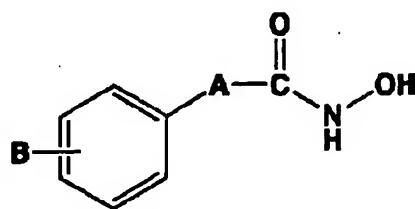
[Table 8] 7 of a Table -1 continuation



化合物番号	B	Bの置換位置	A
71		m	
72		m	
73		m	
74		m	
75		m	
76		p	
77		p	
78		p	
79		p	
80		p	

[0035]

[Table 9] 8 of a Table -1 continuation



化合物番号	B	B の置換位置	A
81		m	
82		m	
83		m	
84		m	
85		m	
86		m	

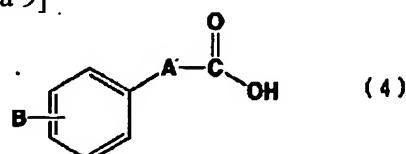
B の置換位置で m はメタ位を、 p はパラ位を表わす

The compound of this invention can be manufactured, for example by the following approaches.

(a) a general formula -- (4) [-izing 9]

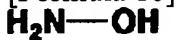
[0036]

[Formula 9]



[-- the inside of a formula, and A and B -- the above and homonymy.] the compound and formula which are come out of and expressed -- or [ giving the compound expressed with (5 [-izing 10]) to a condensation reaction ] -- [0037]

[Formula 10]

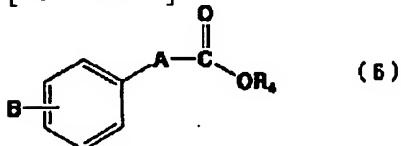


(5)

(b) a general formula -- (6) [-izing 11]

[0038]

[Formula 11]



The inside of [type, and A and B are the above and homonymy. R4 expresses a methyl group, an ethyl group, an iso-propyl group, n-butyl, iso-butyl, benzyl, etc.] It comes out and is obtained by giving the compound expressed with a formula (5) to a substitution reaction to the compound expressed. The compound shown in a general formula (4) and a general formula (6) is marketed, or it is a known compound, and is compounded easily or can be obtained by the approach given in the after-mentioned example.

[0039] The condensation reaction of (a) can be carried out by the approach of the amide bonding reaction in the usual peptide, for example, activity ester, a mixed acid anhydride, or an acid chloride. For example, after carrying out condensation of the N-hydroxy compounds, such as phenols, such as a compound expressed with a general formula (4), 2, 4, 5-trichlorophenol and pentachlorophenol, or 4-nitrophenol, or N-hydroxysuccinimide, and hydroxybenzotriazole, to the bottom of existence of dicyclohexylcarbodiimide and changing them into an activity ester object, it is obtained by making it react with the compound expressed with a formula (5).

[0040] Moreover, after making the compound expressed with a general formula (4) react with ethanedioyl chloride, a thionyl chloride, phosphorus oxychloride, etc. and changing into an acid chloride, it can carry out by carrying out condensation to the compound expressed with a formula (5).

[0041] Moreover, after obtaining a mixed acid anhydride by making it react with the compound expressed with a general formula (4), methyl chlorocarbonate, chloro ethyl carbonate, chloro carbonic acid benzyl, chloro carbonic acid isobutyl or methanesulfonyl chloride, anhydrous trifluoroacetic acid, etc., it is obtained also by condensing with the compound expressed with a formula (5).

[0042] Peptide condensation reagents, such as dicyclohexylcarbodiimide, N, and N'-carbonyldiimidazole, diphenyl phosphoric-acid azide, and cyano diester phosphate, can be independently used for the condensation reaction concerned, and it can also perform them further again.

[0043] A reaction is made to usually react at -20-+50 degrees C for 0.5 to 48 hours. As a solvent used, alcohols or such mixture, such as halogenated hydrocarbon, such as ether, such as aromatic hydrocarbon, such as benzene and toluene, a tetrahydrofuran, dioxane, and ethyl ether, dichloromethane, and chloroform, N,N-dimethylformamide, and a methanol, ethanol, are mentioned. A reaction rate can also be increased by adding an organic base, for example, triethylamine, or a pyridine, 4-(N and N-dimethyl) aminopyridine, etc.

[0044] The substitution reaction of (b) can be performed by making the compound expressed with a formula (5) by the compound expressed with a general formula (6) react. A reaction is usually the range of the reflux temperature of -20 degrees C - a solvent, and is made to react for 0.5 to 100 hours. As a solvent used, alcohols or such mixture, such as halogenated hydrocarbon, such as ether, such as aromatic hydrocarbon, such as benzene and toluene, a tetrahydrofuran, dioxane, and ethyl ether, dichloromethane, and chloroform, N,N-dimethylformamide, and a methanol, ethanol, iso-propanol, are mentioned.

[0045] As for this reaction, a reaction is accelerated by existence of a base. Inorganic bases, such as

alkoxide bases, such as organic bases, such as an excessive amount of the compound shown by the formula (5) as a base to be used, triethylamine, and a pyridine, sodium methoxide, and a sodium ethoxide, potassium carbonate, a sodium carbonate, and a lithium carbonate, are mentioned.

[0046] The compound expressed with a general formula (1) can form a salt easily with the base permitted in pharmacology. As the base, organic bases, such as inorganic bases, such as a lithium, sodium, a potassium, magnesium, calcium, and ammonium, and monomethylamine, ethylamine, benzylamine, can be mentioned. These salts as well as the compound of the general formula (1) of a molecular corpuscle can be used as an active principle compound of this invention. Isolation purification of the compound expressed with a general formula (1) can be carried out from a reaction mixture by approaches, such as the usual separation means, for example, an extraction method, the recrystallizing method, and a column chromatography.

[0047] The new hydroxamic acid derivative of this invention has the differentiation-inducing operation of a cell, and is useful as therapy / improvement agents, such as a malignant tumor, an autoimmune disease, and a dermatosis. As a malignant tumor here Acute leukemia, chronic leukemia, a malignant lymphoma, a multiple myeloma, Hematopoietic organ neoplasms, such as a macroglobulinemia, colon cancer, rectal cancer, colon cancer, A brain tumor, head neck cancer, a breast cancer, lung cancer, an esophagus cancer, gastric cancer, hepatic carcinoma, gallbladder cancer, a cholangioma, A pancreatic cancer, islet cell cancer, renal cell carcinoma, adrenal cortical adenocarcinoma, vesical cancer, a prostatic cancer, the orchioncus, An ovarian cancer, a uterine cancer, a choriocarcinoma, a thyroid cancer, a carcinoid-type-bronchial-adenoma neoplasm, skin carcinoma, Solid neoplasms, such as a malignant melanoma, an osteosarcoma, a soft tissue sarcoma, a neuroblastoma, a Wilms' tumor, and a retinoblastoma, are mentioned, with an autoimmune disease, rheumatism, a nephritis, diabetes mellitus, etc. are mentioned and the acne and eczema which cannot be dried as a dermatosis, atopic dermatitis, etc. are mentioned. In addition, the object disease of this invention is not limited to these.

[0048] The active principle compound of this invention is useful as drugs, and these are used with the gestalt of common medical pharmaceutical preparation. Pharmaceutical preparation is prepared using a diluent or excipients, such as the bulking agent usually used, an extending agent, a binder, moisture adhesive material, disintegrator, a surfactant, and lubricant. As this physic pharmaceutical preparation, various kinds of gestalten can choose according to the therapy purpose, and a tablet, a pill, powder, liquids and solutions, suspension, an emulsion, a granule, a capsule, suppositories, and injections (liquids and solutions, suspension, etc.) are mentioned as that typical thing.

[0049] It faces fabricating in the gestalt of a tablet and various kinds of things known better than before can be widely used in this field as support. As the example, for example A lactose, white soft sugar, a sodium chloride, grape sugar, starch, Excipients, such as a calcium carbonate, a kaolin, crystalline cellulose, and a silicic acid, water, Ethanol, propanol, simple syrup, grape-sugar liquid, starch liquid, A gelatin solution, carmellose liquid, a shellac, methyl cellulose, potassium phosphate, Binders, such as a polyvinyl pyrrolidone, desiccation starch, carmellose calcium, Sodium alginate, agar powder, a sodium hydrogencarbonate, a calcium carbonate, Polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, Disintegrator, such as a stearin acid monoglyceride, starch, and a lactose, white soft sugar, stearin acid, Collapse inhibitors, such as cocoa butter and hydrogenated oil, a quarternary-ammonium-salt radical, Lubricant, such as a polyethylene glycol, etc. can be used in adsorbents, such as moisturizers, such as absorption enhancers, such as sodium lauryl sulfate, a glycerol, and starch, starch, a lactose, a kaolin, a bentonite, and a colloid silicic acid, talc, a stearate, and the end of a boric acid. Furthermore, a tablet can be used as the tablet which gave the usual coating if needed, for example, a sugar-coated tablet, a gelatin encapsulation lock, an enteric tablet, a film coated tablet or a bilayer lock, and a multilayered tablet.

[0050] It faces fabricating in the gestalt of a pill and a well-known thing can be conventionally used widely in this field as support. As the example, various additives, such as binders, such as excipients, such as grape sugar, a lactose, starch, cacao butter, hardening vegetable oil, a kaolin, and talc, gummi arabicum pulveratum, powdered tragacanth, and gelatin, carmellose calcium, and agar, can be used, for example, and it can pharmaceutical-preparation-ize with a conventional method.

[0051] It faces fabricating in the gestalt of suppositories and a well-known thing can be conventionally used widely as support. As the example, the ester of a polyethylene glycol, cacao butter, higher alcohol, and higher alcohol, gelatin, semisynthetic glyceride, etc. can be mentioned, for example.

[0052] A capsule is mixed with various kinds of support which usually illustrated the active principle compound above according to the conventional method, and a hard gelatine capsule, an elasticity capsule, etc. are filled up with it, and it is prepared.

[0053] When preparing as injections, liquids and solutions, an emulsion, and suspension are sterilized, and it is desirable that they are blood and an isotonicity, it can face fabricating in these gestalten and what is commonly used in this field as a diluent, for example, water, ethanol, macro gall, propylene glycol, ethoxylation isostearyl alcohol, polyoxy-ized isostearyl alcohol, and polyoxyethylene sorbitan fatty acid ester can be used. In this case, the salt, the grape sugar, or the glycerol of sufficient amount to prepare an isosmotic solution may be made to contain in physic pharmaceutical preparation, and the usual solubilizing agent, a buffer, an aponia-ized agent, etc. may be added.

[0054] A coloring agent, a preservative, perfume, a flavor agent, a sweetening agent, etc. and other drugs can also be made to contain in physic pharmaceutical preparation if needed furthermore.

[0055] Although especially the amount of the active principle compound which should be contained in these physic pharmaceutical preparation of this invention is suitably chosen from a large area, without being limited, it is usually about 5 - 50 % of the weight preferably about one to 70% of the weight in a pharmaceutical preparation constituent.

[0056] Especially a limit does not have the medication method of these physic pharmaceutical preparation of this invention, and a medicine is prescribed for the patient by the approach according to extent of various formulation, a patient's age, sex, and a disease, and other conditions. for example, in the case of a tablet, a pill, liquids and solutions, suspension, an emulsion, a granule, and a capsule, it administers orally -- having -- the case of injections -- independent -- or it mixes with the usual water additions, such as grape sugar and amino acid, and administers intravenously -- having -- further -- the need -- responding -- independent -- intramuscular and hypodermically -- or intraperitoneal administration is carried out. Intrarectal administration of the case of suppositories is carried out.

[0057] Although the dose of these physic pharmaceutical preparation of this invention is suitably chosen by extent of direction for use, a patient's age, sex, and a disease, and other conditions, it is good for the amount of an active principle compound to usually set to about about 0.0001-100mg per weight per day of 1kg. Moreover, it is desirable for an active principle compound to contain in about 0.001-1,000mg in the pharmaceutical preparation of administration unit form voice. The compound expressed with the general formula (1) of this invention or its salt does not show toxicity in the dose which takes effect in pharmacology.

[0058]

[Example] Although an example and the example of a pharmacological test explain this invention below at a detail, this invention is not limited to these. In addition, the number in the parenthesis of a title is a number of the compound illustrated to detailed explanation.

[0059] Example 1 Composition of 3-[4-(N and N-dimethyl) amino] benzoylcinnamohydrozamic acid (Table -1: compound number 5) (1-1) They are ethylene glycol 13.6g (219mmol) and pyridinium to a 3-BUROMO benzaldehyde 35.3g (190mmol) toluene (200ml) solution. 2.5g (10mmol) of p-toluene sulfonate was added, and heating reflux was carried out for 5 hours, removing the moisture generated using Dean Stark. 2-(3-BUROMO phenyl)-1 and 3-dioxolane 35.02g (80.1% of yield) was obtained as a colorless oily liquid by separating a part for the solid-state which deposited after radiationnal cooling, and distilling the residue which distilled off and obtained the solvent under reduced pressure.

bp.107-109 degree-C/2mmHg 1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:4.00-4.16 (4H, m), 5.79 (1H, s), 7.25 (1H, dd, J = 8 or 8Hz), 7.40 (1H, d, J= 8Hz), 7.49 (1H, d, J= 8Hz), 7.64(1H, s). [0060] (1-2) After thionyl chloride 17.85g (150mmol) was dropped at the toluene (300ml) suspension of 16.5g (100mmol) of 4-(N and N-dimethyl) aminobenzoic acids at the room temperature, heating stirring was carried out at 80 degrees C for 2 hours. Toluene after distilling off a solvent and superfluous thionyl chloride (300ml) - It suspended in THF (100ml) and acid chloride suspension was prepared. This suspension was cooled

at -70--78 degree C under the nitrogen air current. On the other hand, warming to magnesium 2.94g (121mmol) THF (100ml) suspension, the THF (40ml) solution of 24.2g (110mmol) of compounds obtained at the process (1-1) was dropped, and the Grignard reagent of dark brown was prepared. The Grignard reagent prepared previously was dropped at the suspension of acid chloride under the nitrogen air current, maintaining -70--78 degree C.

[0061] It stirred under ice-cooling further at -70--78 degree C after dropping for 1 hour for 2 hours. The saturated ammonium chloride solution was added to the solution of this yellow orange, and it stirred for 1 hour. It stirred for 1 hour, after adding the sulfuric-acid water solution 5 more% and making it about one pH. After the sodium-hydroxide water solution neutralized, ethyl acetate extracted. It dried, after water and saturation brine washed the organic layer. After having distilled off the solvent, and the methanol's having washed the obtained residue and removing an unreacted raw material, the silica gel column chromatography (chloroform: ethyl-acetate =10:1) refined, and 3-[4-(N and N-dimethyl) amino] benzoyl benzaldehyde 13.5g (53% of yield) was obtained as yellow oily matter.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:3.10 (6H, s), 6.70 (2H, d, J= 8.8Hz) 7.64 (1H, dd, H= 7.3, 8.1Hz), 7.78 (2H, d, J= 8.8Hz), 7.99 (1H, d, J= 8.1Hz), 8.06 (1H, d, J= 7.3Hz), 8.20 (1H, s), 10.08(1H, s). [0062] (1-3) Bottom of nitrogen air current ethoxy carbonylmethyl (triphenyl) phosphine ylide 22.74g (65.3mmol) was added to the toluene (300ml) suspension of 12.81g (50.2mmol) of compounds obtained at the process (1-2), and heating stirring was carried out at 90-100 degrees C under the nitrogen air current for 9 hours. It diluted with ethyl acetate after radiationnal cooling, and water and saturation brine washed. A solvent is distilled off after drying an organic layer, a silica gel column chromatography (n-hexane: ethyl-acetate =2:1) refines the obtained residue, and it is ethyl. 3-[4-(N and N-dimethyl) amino] benzoyl cinnamate 13.38g (82.4% of yield) was obtained as a yellow wax-like solid-state.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:1.34 (3H, t, J= 7.3Hz), 3.10 (6H, s) 4.27 (2H, q, J= 7.3Hz), 6.48 (1H, d, J= 16.1Hz) 6.69 (2H, d, J= 8.8Hz), 7.48 (1H, m), 7.68 (1H, d, J= 8.8Hz), 7.74 (1H, d, J= 8.8Hz), 7.82 (2H, d, J= 8.8Hz), 7.83(1H, d, J= 15.4Hz). [0063] (1-4) 2.7ml (1.35mmol) of 0.5-N lithium-hydroxide water solutions was added to the methanol (10ml) solution of 0.33g (1.02mmol) of compounds obtained at the process (1-3) at the room temperature, and it stirred, warming at 40 degrees C for 10 hours. After radiationnal cooling, ethyl acetate extracted, after adding 1-N hydrochloric-acid water solution and neutralizing. 0.18g (59.9% of yield) of 3-[4-(N and N-dimethyl) amino] benzoyl cinnamic acid was obtained as a yellow solid-state by distilling off desiccation and a solvent for an organic layer after washing with saturation brine.

mp.153-160 degree-C1 H-NMR(270MHz, DMSO-d6) deltappm:3.05 (6H, s), 6.59 (1H, d, J= 16.1Hz), 6.78 (1H, d, J= 8.8Hz), 7.56-7.70 (6H, m), 7.86 (1H, s), 7.92 (1H, d, J= 8.1Hz), 12.46(1H, br.s). [0064] (1-5) Triethylamine 0.07ml (0.5mmol) was added to the THF (2ml) solution of 125mg (0.425mmol) of compounds obtained at the process (1-4), and further, bottom chloro carbonic acid isobutyl of ice-cooling 0.07ml (0.54mmol) was added slowly, and was stirred under ice-cooling. Triethylamine 0.2ml (1.43mmol) was added to the obtained suspension after 2-hour stirring, 0.10g (1.44mmol) of hydroxylamine hydrochlorides was added further, and it stirred under ice-cooling for 2.5 hours. After it added saturation sodium bicarbonate water and ethyl acetate extracted, saturation brine washed the obtained organic layer, the silica gel column chromatography (dichloromethane: methanol =8:1) refined further desiccation and the residue obtained by carrying out solvent distilling off, and 19mg (14% of yield) of 3-[4-(N and N-dimethyl) amino] benzoylcinnamohydrozamic acid was obtained as a blackish brown solid-state.

mp.174-177 degree-C(dec.) 1 H-NMR(270MHz, DMSO-d6) deltappm:3.05 (6H, s), 6.53 (1H, d, J= 16.1Hz), 6.78 (2H, d, J= 8.8Hz), 7.5-7.9 (7H, m), 9.09 (1H, s), 10.76(1H, s). [0065] Example 2 Composition of 3-benzoylcinnamohydrozamic acid (Table 1: compound 1) (2-1) The THF (5ml) solution of 5.04g (22mmol) of compounds obtained at the process (1-1) was gradually dropped at magnesium 0.59g (24.2mmol) THF (5ml) suspension, and the Grignard reagent was prepared. The benzoyl chloride 2.81g (20mmol) THF (20ml) solution was cooled at -70--78 degree C under the nitrogen air current, and the Grignard reagent prepared previously was dropped over 30 minutes, maintaining -70--78 degree C. After stirring then for 1 hour, it stirred under ice-cooling for 2 hours.

After having added the saturated ammonium chloride solution, adding the sulfuric-acid water solution 5% after the reaction halt and making it about one pH, it was left at the room temperature overnight. After ethyl acetate extracted, saturation sodium bicarbonate water and saturation brine washed all organic layers, the silica gel column chromatography (n-hexane: ethyl-acetate =8:1) refined desiccation and the obtained residue which carried out solvent distilling off, and 3-benzoyl benzaldehyde 1.70g (40.4% of yield) was obtained as light yellow oil.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:7.45-7.55 (2H, m), 7.61-7.71 (2H, m), 7.82 (2H, dd, J= 1.5, 7.3Hz), 8.08-8.14 (2H, m), 8.29 (1H, d, J= 1.5Hz), 10.10(1H, s). [0066] (2-2) Ethoxy carbonylmethyl (triphenyl) phosphine ylide 3.35g (9.58mmol) was added to the toluene (37ml) solution of 1.55g (7.3mmol) of compounds obtained at the process (2-1), and heating stirring was carried out at 100 degrees C for 4 hours. A silica gel column chromatography (n-hexane: ethyl-acetate =8:1) refines the residue obtained by distilling off a solvent, and it is ethyl 3-benzoyl cinnamate 2.05g (99% of yield) was obtained as light yellow oil.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:1.34 (3H, t, J= 7.3Hz), 4.27 (2H, q, J= 7.3Hz), 6.48 (1H, d, J= 15.1Hz), 7.4-8.0(10H, m). [0067] (2-3) The water (20ml) solution of 0.39g of a lithium hydroxide and 1 hydrates (9.36mmol) was added to the methanol (25ml) solution of 1.75g (6.24mmol) of compounds obtained at the process (2-2), and it stirred at 40 degrees C for 3 hours. Ethyl acetate extracted, after making it acidity in a hydrochloric-acid water solution 10%. After water and saturation brine washed all organic layers, 1.03g (65.4% of yield) of 3-benzoyl cinnamic acid was obtained as a white solid-state by washing desiccation and the residue obtained by carrying out solvent distilling off with ethyl ether.

mp.157-159 degree-C1 H-NMR(270MHz, DMSO-d<sub>6</sub>) deltappm:6.57 (1H, d, J= 16.1Hz), 7.54-7.79 (8H, m), 7.96-7.99 (2H, m), 12.41(1H, br.s). [0068] (2-4) Chloro carbonic acid isobutyl 0.17ml (1.3mmol) was added having added triethylamine 0.19ml (1.3mmol) to the THF (5ml) solution of 0.25g (1.0mmol) of compounds obtained at the process (2-3), and maintaining -10--20 degree C at it, and it stirred for 30 minutes. 0.35g [ of bottom hydroxylamine hydrochlorides of ice-cooling ] (5.0mmol) and triethylamine 0.70ml (5.0mmol) was added to the reaction mixture which became cloudy, and it stirred for two days at the room temperature. Chloroform extracted, after making it acidity with 1-N hydrochloric acid. After saturation brine washed the organic layer, 0.10g (37.4% of yield) of 3-benzoylcinnamohydrozamic acid was obtained as a white crystal by a silica gel column chromatography's (methanol's: chloroform's :s acetic-acid ='s 15:1:0.'s1) refining desiccation and the residue obtained by carrying out solvent distilling off, and crystallizing with ethyl-acetate-ethyl ether further.

mp.157-159 degree-C(dec.) 1 H-NMR(270MHz, DMSO-d<sub>6</sub>) deltappm:6.55 (1H, d, J= 15.4Hz), 7.51-7.93 (10H, m), 9.26 (1H, br.s), 10.71(1H, br.s).IR(KBr) cm-1:3459, 3298, 1670, 1648, 1625, 1521, 1431, 1296 and 1058, 978. [0069] Example 3 Composition of 4-[4-(N and N-dimethyl) amino] benzoylcinnamohydrozamic acid (Table -1: compound number 10) (3-1) It is pyridinium to a 4-BUROMO benzaldehyde 25.0g (135.1mmol) toluene (100ml) solution. 2.5g (10mmol) of p-toluene sulfonate was added, ethylene glycol 10.06g (162.1mmol) was added further, and heating reflux was carried out for 4 hours, removing the water generated by Dean Stark. After separating and removing the depositing solid-state after radiationnal cooling and distilling off a solvent, 2-(4-BUROMO phenyl)-1 and 3-dioxolane 25.83g (83.4% of yield) was obtained as a colorless oily liquid by distilling under reduced pressure.

bp.135-138 degree-C/1mmHg1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:3.97-4.16 (4H, m), 5.77 (1H, s), 7.35 (2H, d, J= 8.1Hz), 7.51(2H, d, J= 8.1Hz). [0070] (3-2) Iodine was added to magnesium 0.95g (39mmol) THF (30ml) suspension one cup of micro spatula as an activator. The THF (10ml) solution of 7.02g (36mmol) of compounds obtained at the process (3-1) was added carefully, warming magnesium suspension. When foaming started on the way, after stopping heating and adding the remainder further, it stirred at the room temperature for 2 hours, and the dark-brown Grignard solution was prepared. [0071] Thionyl chloride 5.35g (45mmol) was added to the toluene (100ml) suspension of 4.95g (30mmol) of 4-(N and N-dimethyl) aminobenzoic acids, and heating stirring was carried out at 100 degrees C for 2 hours. After distilling off a solvent, THF (100ml) and toluene (150ml) were added twice to the residue except superfluous thionyl chloride with azeotropy with toluene. After cooling this

reaction mixture so that it may become -70--78 degree C, the Grignard reagent prepared previously was dropped adjusting so that an internal temperature may become -65--78 degree C. It ice-cooled, after stirring at -70--75 degree C for 1 hour, after dropping and, and the temperature up was carried out over 2 hours from under ice-cooling to the room temperature.

[0072] After suspending a reaction by the saturated ammonium chloride solution, it was made about one pH in the sulfuric-acid water solution 5%, and stirred at the room temperature for 1 hour. Ethyl acetate extracted, after making it alkalinity in a sodium-hydroxide water solution. Sodium bicarbonate water and saturation brine refined the organic layer, the silica gel column chromatography (chloroform: ethyl-acetate =10:1) refined desiccation and the residue obtained by carrying out solvent distilling off after washing, and 4-(N and N-dimethyl) amino benzoyl benzaldehyde 2.82g (37.1% of yield) was obtained as a yellow wax-like solid-state.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:3.09 (6H, s), 6.68 (2H, d, J= 8.8Hz), 7.77 (2H, d, J= 9Hz), 7.83 (2H, d, J= 8.1Hz), 7.97 (2H, d, J= 8.1Hz), 10.11(1H, s). [0073] (3-3) Toluene (20ml) was made to suspend 1.01g [ of compounds ] (4.00mmol), and ethoxy carbonylmethyl (triphenyl) phosphine ylide 1.81g (5.2mmol) obtained at the process (3-2), and heating stirring was carried out at 80 degrees C under the nitrogen air current for 5 hours.. It dilutes with ethyl acetate after radiationnal cooling, water and saturation brine refine after washing desiccation and the residue obtained by carrying out solvent distilling off with a silica gel column chromatography (chloroform: ethyl-acetate =10:1), and it is ethyl 4-(N and N-dimethyl) amino benzoyl cinnamate 1.03g (79.6% of yield) was obtained as a yellow solid-state.

mp.130-131 degree-C1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:1.35 (3H, t, J= 7.3Hz), 3.08 (6H, s), 4.28 (2H, q, J= 7.3Hz), 6.52 (1H, d, J= 15.1Hz), 6.68 (2H, d, J= 8.8Hz), 7.60 (2H, d, J= 8.1Hz), 7.70-7.80 (5H, m). [0074] (3-4) the methanol (20ml)-water (20ml) suspension of 0.97g (3.0mmol) of compounds obtained at the process (3-3) -- 0.19g (4.5mmol) of a lithium hydroxide and 1 hydrates -- adding -- 40 degrees C -- 9 hours -- warming -- it stirred. After making it acidity in 1-N hydrochloric-acid water solution, it extracted by the methyl ethyl ketone. Saturation brine washed the organic layer, methanol-diisopropyl ether washed desiccation after washing, and the solid-state obtained by carrying out solvent distilling off, and 0.62g (70% of yield) of 4-(N and N-dimethylamino) benzoyl cinnamic acid was obtained as a brown solid-state by drying.

mp.211-215 degree-C(dec.) 1 H-NMR(270MHz, DMSO-d6) deltappm:3.05 (6H, s), 6.66 (1H, d, J= 15Hz) 6.79 (2H, d, J= 8Hz), 7.63-7.69 (5H, m), 7.83(2H, d, J= 8Hz).IR(KBr) cm-1:3420, 2582(br), 1697, 1648, 1605, 1282, 986, 933, 773 [0075] (3-5) Having added triethylamine 0.093ml (0.66mmol) to the THF (3ml) suspension of 0.19g (0.64mmol) of compounds obtained at the process (3-4), and cooling by \*\*\*\* further, chloro carbonic acid isobutyl 0.086ml (0.66mmol) was added, and it stirred under ice-cooling for 15 minutes. After having added 0.23g (3.3mmol) of bottom hydroxylamine hydrochlorides of ice-cooling, adding triethylamine 0.46ml (3.3mmol) further and leaving it in a refrigerator below 4 degrees C overnight, it stirred for two days at the room temperature. After adding water and stopping a reaction, it extracted by the methyl ethyl ketone. Saturation brine refined the organic layer, the silica gel column chromatography (chloroform: methanol =10:1) refined desiccation and the residue obtained by carrying out solvent distilling off after washing, and 0.10g (48.8%) of 4-[4-(N and N-dimethyl) amino] benzoylcinnamohydrozamic acid was obtained as a light brown solid-state.

mp.amorphous solid.1 H-NMR(270MHz, DMSO-d6) deltappm:3.05 (6H, s), 6.58 (1H, d, J= 15Hz) 6.78 (2H, d, J= 8.8Hz), 7.54 (1H, d, J= 15Hz) 7.64-7.68 (6H, m), 9.11 (1H, br.s), 10.85(1H, br.s).IR(KBr) cm-1:3258(br), 1636, 1593, 1541, 1374, 1322, 1289, 1200, 1178 and 1147, 929. [0076] Oxalyl chloride 0.7ml (8.0mmol) was added to the dichloromethane (10ml) solution of 0.70g (3.12mmol) of synthetic 4-phenyl cinnamic acid of example 4 4-phenyl SHINNAMO hydroxamic acid (Table 1: compound number 19), and one drop of DMF was dropped further. After foaming stopped, it stirred at 40 degrees C for 1.5 hours. After having carried out azeotropy with toluene after carrying out reduced pressure distilling off of the solvent, and removing a superfluous oxalyl chloride, it dissolved in dichloromethane (10ml) again. Saturation sodium bicarbonate water (2ml) was added to the THF (5ml) suspension of 1.0g of hydroxylamine hydrochlorides (14.4mmol), and it was left for 10 minutes. After adding this

THF layer to a previous dichloromethane solution at a stretch, it stirred violently for 1.5 hours. [0077] After making it acidity in 1-N hydrochloric-acid water solution, it extracted by ethyl acetate (2 times) and the methyl ethyl ketone (1 time). After water and saturation brine washed all organic layers, 0.57g (76.3% of yield) of 4-phenyl SHINNAMO hydroxamic acid was obtained as a light brown crystal by crystallizing desiccation and the obtained residue which carried out solvent distilling off from chloroform.

mp.171-173 degree-C1 H-NMR(270MHz, DMSO-d6) deltappm:6.52 (1H, d, 15.1Hz), 7.3-7.8 (10H, m), 9.07 (1H, br.s), 10.79(1H, br.s).Anal.Calcd.C15H13NO2 0.1H2O C:74.18, H:5.56, N:5.77. Found C:74.22, H:5.50, N:5.68. [0078] Example 5 Composition of 3-{4-[N-(2-aminophenyl) amino] carbonyl} phenylpropiohydroxamic acid (Table 1: compound number 48) (5-1) Thionyl chloride 12.0ml (164mmol) was added to the toluene (100ml) suspension of 15.0g of terephthal aldehydic acid (100mmol), and heating stirring was carried out at 90 degrees C for 1.5 hours. After radiationnal cooling, after making the residue obtained by carrying out reduced pressure distilling off of a solvent and the superfluous thionyl chloride add and suspend dioxane (20ml), 2-nitroaniline 13.8g (100mmol) was added, and heating reflux was carried out for 6 hours. The solid-state which deposited by distilling off a solvent after separating the depositing solid-state after radiationnal cooling, and adding a methanol and an acetone to the obtained residue was separated, it dried, and N-(2-nitrophenyl)-4-formyl benzamide 15.41g (57.0% of yield) was obtained as a yellow solid-state.

1 H-NMR(270MHz, DMSO-d6) deltappm:7.43-7.49 (1H, m), 7.77-7.79 (2H, m), 8.03 (1H, d, J= 8.8Hz), 8.10 (2H, d, J= 8.8Hz) 8.15 (2H, d, J= 8.8Hz), 10.13 (1H, s), 10.96(1H, br.s).IR(KBr) cm-1:3357, 1706, 1672, 1607, 1588, 1508, 1341, 1277 and 1147, 855. [0079] (5-2) Ethoxy carbonylmethyl (triphenyl) phosphine ylide 2.51g (7.21mmol) was added to the toluene (25ml) suspension of 1.50g (5.50mmol) of compounds obtained at the process (5-1), and heating stirring was carried out at 80 degrees C under the nitrogen air current for 9 hours. After radiationnal cooling, reaction mixture was diluted with ethyl acetate and after [ washing ] desiccation and a solvent were distilled off with water and saturation brine. A silica gel column chromatography (dichloromethane: ethyl-acetate =10:1) refines the obtained residue, and it is ethyl. 3-{4-[N-(2-nitrophenyl) amino] carbonyl phenyl} PUROENOETO 1.70g (90.0% of yield) was obtained as a yellow solid-state (cis--transformer 1:1 mixture). 1 H-NMR (270MHz, CDCl<sub>3</sub>) deltappm:1.26 (3H, t, J= 3Hz), 1.36 (3H, t, J= 7.3Hz) 4.19 (2H, q, J= 7.3Hz), 4.30 (2H, q, J= 7.3Hz) 6.08 (1H, d, J= 12.5Hz), 6.55 (1H, d, J= 15.4Hz) 7.01 (1H, d, J= 12.5Hz), 7.2-7.3 (3H, m), 7.67-7.76 (6H, m), 7.97- 8.04 (4H, m) and 8.30 (2H, dd, J= 6.7, 1.5Hz) -- 9.01(2H, dd, J= 7.3, 1.5Hz).IR(KBr) cm-1:3374, 1716, 1684, 1640, 1606, 1583, 1498, 1432, 1337, 1254, 1177 and 1041, 849. [0080] (5-3) After suspending 0.70g (2.06mmol) of compounds obtained at the process (5-2) in a THF(25ml)-methanol (25ml), hydrogenation was performed by making palladium carbon (0.1g) into a catalyst 10%. It is ethyl by filtering a catalyst and washing with a methanol the residue obtained by distilling off a solvent after reaction termination. 3-{4-[N-(2-aminophenyl) amino] carbonyl phenyl} propanoate 0.46g (71.5% of yield) was obtained as a white solid-state.

mp.94-96 degree-C1 H-NMR(270MHz, DMSO-d6) deltappm:1.17 (3H, t, J= 7.3Hz), 2.66 (2H, t, J= 7.3Hz) 2.93 (2H, t, J= 7.3Hz), 4.05 (2H, q, J= 7.3Hz) 4.87 (2H, br.s), 6.60 (1H, dd, J= 7.3, 8.1Hz) 6.79 (1H, d, J= 8.1Hz), 6.97 (1H, dd, J= 7.3, 8.1Hz) 7.17 (1H, d, J= 8.1Hz), 7.35 (2H, d, J= 8.1Hz) 7.91 (2H, d, J= 8.1Hz), 9.62(1H, s).IR(KBr) cm-1:3394, 3345, 1723, 1638, 1606, 1524, 1490, 1457, 1299 and 1185, and 746.Anal.Calcd.C18H20N2O3.0.1H2O C:68.81, H:6.48, N:8.91. Found C:69.21, H:6.45, N:8.97. [0081] (5-4) 0.4g [ of hydroxylamine hydrochlorides ] (5.75mmol) and sodium-ethoxide 0.4g (5.88mmol) was added to the ethanol (10ml) suspension of 0.20g (0.64mmol) of compounds obtained at the process (5-3), and heating reflux was carried out for 5 hours. After adding water and dissolving, saturation brine was added and it extracted by ethyl acetate and the methyl ethyl ketone. By carrying out after [ desiccation ] solvent distilling off of the organic layer, 0.11g (54% of yield) of 3-{4-[N-(2-aminophenyl) aminocarbonyl] phenyl} propione hydroxamic acid was obtained as a light brown solid-state.

mp.amorphous solid1 H-NMR(270MHz, DMSO-d6) deltappm:2.32 (2H, t, J= 7.3Hz), 2.89 (2H, t, J= 7.3Hz) 4.90 (2H, s), 6.60 (1H, dd, J= 7.3, 7.3Hz) 6.78 (1H, d, J= 6.6Hz), 6.96 (1H, dd, J= 7.3, 7.3Hz)

7.16 (1H, d, J= 8.1), 7.33 (2H, d, J= 8.1Hz), 7.91 (2H, d, J= 8.1Hz), 9.66 (1H, s), 10.23 (1H, s), 10.47 (1H, br.s). [0082] Example 1 of a pharmacological test It is known that the rise of the differentiation-inducing operation trial alkaline phosphatase (ALP) activity over Homo sapiens ovarian cancer origin A2780 cell will be known as an index of differentiation of a Homo sapiens colon cancer cell, for example, butanoic acid sodium will raise ALP activity (Young;Cancer Res., 45 and 2976 (1985), Morita;Cancer Res., and [42, 4540] (1982)). Then, the differentiation-inducing operation against an index by ALP activity was evaluated.

[0083] (The experiment approach) It wound 0.1ml of A2780 cells at a time so that it might become 96 hole plate with 15000 piece / well, and it added at a time 0.1ml of solutions of the test drug which carried out phase dilution in the culture medium on the next day. The TBS buffer solution (20mMTris, 137mM NaCl, pH7.6) washed the cell on a plate twice after culture for three days. Subsequently, 0.6mg/ml It added 0.05ml (9.6% diethanolamine, 0.5mM MgCl<sub>2</sub> (pH9.6)) of p-nitrophenylphosphate at a time, and incubated at the room temperature for 30 minutes. 3Ns After suspending a reaction by 0.05ml of NaOH solutions, the absorbance of 405nm was measured and it asked for the minimum concentration (ALPmin) of the drug with which the rise of ALP activity is caused.

(Experimental result) The example of representation of an experimental result was shown in Table -2 [Table 10].

[0084]

[Table 10]

Table-2: The differentiation-inducing operation sample offering compound to A2780 cell ALPmin (muM) ----- The compound of an example 1 The compound of one example 2 Compound of three examples 3 Compound of one example 4 Compound of 30 examples 5 10 butanoic-acid sodium 10,000 [0085]

[Effect of the Invention] The new hydroxamic acid derivative of this invention has a strong differentiation-inducing operation. Therefore, usefulness is expected as a hematopoietic organ neoplasm, a solid carcinoma, an autoimmune disease, and a therapy / improvement medicine of a dermatosis.

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**TECHNICAL FIELD**

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[Industrial Application] This invention relates to a new hydroxamic acid derivative. It is related with use in the anticancer agent and drugs based on a differentiation-inducing operation of a new hydroxamic acid derivative in more detail.

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**PRIOR ART**

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[Description of the Prior Art] By the time the death by current and cancer extracts death by the heart disease and the cerebrovascular disease and occupies a primacy in a cause of death, it will have become. On the other hand, research of various cures, such as a surgical operation, radiotherapy, a thermotherapy, and a chemotherapy, has so far been done for ascendancy of cancer. Although a chemotherapy is one of the big columns of cancer treatment and many drugs have been found out especially until now, though regrettable, the present condition is drugs' satisfying enough not being found out but waiting eagerly for new drugs, also including a side effect till today.

[0003] Many anticancer agents found out so far used the cancer cell itself as the target, and have been chosen for the purpose of killing all the cells that became cancer. It was what demonstrates the carcinostatic effectiveness by carrying out a direct action to DNA in a cancer cell, and making the killer cell effectiveness discover as the device. However, these anticancer agents were lacking in the selectivity of a cancer cell and a normal cell, and the side effect discovered in a normal cell as a result became a limitation on a therapy in many cases.

[0004] On the other hand, the differentiaion inducer aims at controlling the property (reproductive integrity) which the cancer cell instead of the direct killer cell effectiveness has, and urging differentiation to a cancer cell also in the anticancer agent. Since various check devices act on the cell which specialized and it is led to a natural death of a cell, finally it may happen to growth control of a cancer cell, and the regression of cancer. Although it is not the anticancer agent which has the killer cell effectiveness in respect of the regression of cancer because of the mechanism of a differentiation-inducing operation, selectivity with a normal cell, low toxicity, etc. are expectable by one side. [by which it is known well that the retinoic acid which is a differentiaion inducer is actually used for a therapy, and high effectiveness is shown by the myelogenous leukemia before acute -- Huang et al. --;Blood, 72,567-572 (1988), Castaign et al. --;Blood, and 76 and 1704 --] besides -1709 (1990) or Warrell;New Engl.J.Med., 324, and 1385-1393 (1991).

[0005] Moreover, since a vitamin D derivative shows a differentiation-inducing operation, many application to an anticancer agent is also studied [others [ 5867 / Olsson;Cancer Res., 43, and / (1983) / 5862-]]. In response to these researches, the application to anticancer agents, such as the vitamin D derivative (JP,6-179622,A) which is a differentiaion inducer, an isoprene derivative (JP,6-192073,A), a tocopherol (JP,6-256181,A), a quinone derivative (JP,6-305955,A), an un-annular poly isoprenoid (JP,6-316520,A), a benzoic-acid derivative (JP,7-206765,A), and a glycolipid (JP,7-258100,A), is reported. However, there are no drugs which reached sufficient level on cancer treatment, to various kinds of cancers, it is effective and drugs with high safety are strongly desired by these researches.

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**EFFECT OF THE INVENTION**

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[Effect of the Invention] The new hydroxamic acid derivative of this invention has a strong differentiation-inducing operation. Therefore, usefulness is expected as a hematopoietic organ neoplasm, a solid carcinoma, an autoimmune disease, and a therapy / improvement medicine of a dermatosis.

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**TECHNICAL PROBLEM**

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[Problem(s) to be Solved by the Invention] The technical problem of this invention has a differentiation-inducing operation of a cancer cell, and is to offer a compound useful as drugs, such as a malignant tumor, an autoimmune disease, and therapy / improvement medicine of a dermatosis.

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**EXAMPLE**

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[Example] Although an example and the example of a pharmacological test explain this invention below at a detail, this invention is not limited to these. In addition, the number in the parenthesis of a title is a number of the compound illustrated to detailed explanation.

[0059] Example 1 Composition of 3-[4-(N and N-dimethyl) amino] benzoylcinnamohydrozamic acid (Table -1: compound number 5) (1-1) They are ethylene glycol 13.6g (219mmol) and pyridinium to a 3-BUROMO benzaldehyde 35.3g (190mmol) toluene (200ml) solution. 2.5g (10mmol) of p-toluene sulfonate was added, and heating reflux was carried out for 5 hours, removing the moisture generated using Dean Stark. 2-(3-BUROMO phenyl)-1 and 3-dioxolane 35.02g (80.1% of yield) was obtained as a colorless oily liquid by separating a part for the solid-state which deposited after radiationnal cooling, and distilling the residue which distilled off and obtained the solvent under reduced pressure.

bp.107-109 degree-C/2mmHg1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:4.00-4.16 (4H, m), 5.79 (1H, s), 7.25 (1H, dd, J = 8 or 8Hz), 7.40 (1H, d, J= 8Hz), 7.49 (1H, d, J= 8Hz), 7.64(1H, s). [0060] (1-2) After thionyl chloride 17.85g (150mmol) was dropped at the toluene (300ml) suspension of 16.5g (100mmol) of 4-(N and N-dimethyl) aminobenzoic acids at the room temperature, heating stirring was carried out at 80 degrees C for 2 hours. Toluene after distilling off a solvent and superfluous thionyl chloride (300ml) - It suspended in THF (100ml) and acid chloride suspension was prepared. This suspension was cooled at -70--78 degree C under the nitrogen air current. On the other hand, warming to magnesium 2.94g (121mmol) THF (100ml) suspension, the THF (40ml) solution of 24.2g (110mmol) of compounds obtained at the process (1-1) was dropped, and the Grignard reagent of dark brown was prepared. The Grignard reagent prepared previously was dropped at the suspension of acid chloride under the nitrogen air current, maintaining -70--78 degree C.

[0061] It stirred under ice-cooling further at -70--78 degree C after dropping for 1 hour for 2 hours. The saturated ammonium chloride solution was added to the solution of this yellow orange, and it stirred for 1 hour. It stirred for 1 hour, after adding the sulfuric-acid water solution 5 more% and making it about one pH. After the sodium-hydroxide water solution neutralized, ethyl acetate extracted. It dried, after water and saturation brine washed the organic layer. After having distilled off the solvent, and the methanol's having washed the obtained residue and removing an unreacted raw material, the silica gel column chromatography (chloroform: ethyl-acetate =10:1) refined, and 3-[4-(N and N-dimethyl) amino] benzoyl benzaldehyde 13.5g (53% of yield) was obtained as yellow oily matter.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:3.10 (6H, s), 6.70 (2H, d, J= 8.8Hz) 7.64 (1H, dd, H= 7.3, 8.1Hz), 7.78 (2H, d, J= 8.8Hz), 7.99 (1H, d, J= 8.1Hz), 8.06 (1H, d, J= 7.3Hz), 8.20 (1H, s), 10.08(1H, s). [0062] (1-3) Bottom of nitrogen air current ethoxy carbonylmethyl (triphenyl) phosphine ylide 22.74g (65.3mmol) was added to the toluene (300ml) suspension of 12.81g (50.2mmol) of compounds obtained at the process (1-2), and heating stirring was carried out at 90-100 degrees C under the nitrogen air current for 9 hours. It diluted with ethyl acetate after radiationnal cooling, and water and saturation brine washed. A solvent is distilled off after drying an organic layer, a silica gel column chromatography (n-hexane: ethyl-acetate =2:1) refines the obtained residue, and it is ethyl. 3-[4-(N and N-dimethyl) amino] benzoyl cinnamate 13.38g (82.4% of yield) was obtained as a yellow wax-like solid-state.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:1.34 (3H, t, J= 7.3Hz), 3.10 (6H, s) 4.27 (2H, q, J= 7.3Hz), 6.48 (1H, d, J= 16.1Hz) 6.69 (2H, d, J= 8.8Hz), 7.48 (1H, m), 7.68 (1H, d, J= 8.8Hz), 7.74 (1H, d, J= 8.8Hz), 7.82 (2H, d, J= 8.8Hz), 7.83(1H, d, J= 15.4Hz). [0063] (1-4) 2.7ml (1.35mmol) of 0.5-N lithium-hydroxide water solutions was added to the methanol (10ml) solution of 0.33g (1.02mmol) of compounds obtained at the process (1-3) at the room temperature, and it stirred, warming at 40 degrees C for 10 hours. After radiationnal cooling, ethyl acetate extracted, after adding 1-N hydrochloric-acid water solution and neutralizing. 0.18g (59.9% of yield) of 3-[4-(N and N-dimethyl) amino] benzoyl cinnamic acid was obtained as a yellow solid-state by distilling off desiccation and a solvent for an organic layer after washing with saturation brine.

mp.153-160 degree-C1 H-NMR(270MHz, DMSO-d<sub>6</sub>) deltappm:3.05 (6H, s), 6.59 (1H, d, J= 16.1Hz), 6.78 (1H, d, J= 8.8Hz), 7.56-7.70 (6H, m), 7.86 (1H, s), 7.92 (1H, d, J= 8.1Hz), 12.46(1H, br.s). [0064] (1-5) Triethylamine 0.07ml (0.5mmol) was added to the THF (2ml) solution of 125mg (0.425mmol) of compounds obtained at the process (1-4), and further, bottom chloro carbonic acid isobutyl of ice-cooling 0.07ml (0.54mmol) was added slowly, and was stirred under ice-cooling. Triethylamine 0.2ml (1.43mmol) was added to the obtained suspension after 2-hour stirring, 0.10g (1.44mmol) of hydroxylamine hydrochlorides was added further, and it stirred under ice-cooling for 2.5 hours. After it added saturation sodium bicarbonate water and ethyl acetate extracted, saturation brine washed the obtained organic layer, the silica gel column chromatography (dichloromethane: methanol =8:1) refined further desiccation and the residue obtained by carrying out solvent distilling off, and 19mg (14% of yield) of 3-[4-(N and N-dimethyl) amino] benzoylcinnamohydrozamic acid was obtained as a blackish brown solid-state.

mp.174-177 degree-C(dec.) 1 H-NMR(270MHz, DMSO-d<sub>6</sub>) deltappm:3.05 (6H, s), 6.53 (1H, d, J= 16.1Hz), 6.78 (2H, d, J= 8.8Hz), 7.5-7.9 (7H, m), 9.09 (1H, s), 10.76(1H, s). [0065] Example 2 Composition of 3-benzoylcinnamohydrozamic acid (Table 1: compound 1) (2-1) The THF (5ml) solution of 5.04g (22mmol) of compounds obtained at the process (1-1) was gradually dropped at magnesium 0.59g (24.2mmol) THF (5ml) suspension, and the Grignard reagent was prepared. The benzoyl chloride 2.81g (20mmol) THF (20ml) solution was cooled at -70--78 degree C under the nitrogen air current, and the Grignard reagent prepared previously was dropped over 30 minutes, maintaining -70--78 degree C. After stirring then for 1 hour, it stirred under ice-cooling for 2 hours. After having added the saturated ammonium chloride solution, adding the sulfuric-acid water solution 5% after the reaction halt and making it about one pH, it was left at the room temperature overnight. After ethyl acetate extracted, saturation sodium bicarbonate water and saturation brine washed all organic layers, the silica gel column chromatography (n-hexane: ethyl-acetate =8:1) refined desiccation and the obtained residue which carried out solvent distilling off, and 3-benzoyl benzaldehyde 1.70g (40.4% of yield) was obtained as light yellow oil.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:7.45-7.55 (2H, m), 7.61-7.71 (2H, m), 7.82 (2H, dd, J= 1.5, 7.3Hz), 8.08-8.14 (2H, m), 8.29 (1H, d, J= 1.5Hz), 10.10(1H, s). [0066] (2-2) Ethoxy carbonylmethyl (triphenyl) phosphine ylide 3.35g (9.58mmol) was added to the toluene (37ml) solution of 1.55g (7.3mmol) of compounds obtained at the process (2-1), and heating stirring was carried out at 100 degrees C for 4 hours. A silica gel column chromatography (n-hexane: ethyl-acetate =8:1) refines the residue obtained by distilling off a solvent, and it is ethyl. 3-benzoyl cinnamate 2.05g (99% of yield) was obtained as light yellow oil.

1 H-NMR(270MHz, CDCl<sub>3</sub>) deltappm:1.34 (3H, t, J= 7.3Hz), 4.27 (2H, q, J= 7.3Hz), 6.48 (1H, d, J= 15.1Hz), 7.4-8.0(10H, m). [0067] (2-3) The water (20ml) solution of 0.39g of a lithium hydroxide and 1 hydrates (9.36mmol) was added to the methanol (25ml) solution of 1.75g (6.24mmol) of compounds obtained at the process (2-2), and it stirred at 40 degrees C for 3 hours. Ethyl acetate extracted, after making it acidity in a hydrochloric-acid water solution 10%. After water and saturation brine washed all organic layers, 1.03g (65.4% of yield) of 3-benzoyl cinnamic acid was obtained as a white solid-state by washing desiccation and the residue obtained by carrying out solvent distilling off with ethyl ether.

mp.157-159 degree-C1 H-NMR(270MHz, DMSO-d<sub>6</sub>) deltappm:6.57 (1H, d, J= 16.1Hz), 7.54-7.79 (8H, m), 7.96-7.99 (2H, m), 12.41(1H, br.s). [0068] (2-4) Chloro carbonic acid isobutyl 0.17ml (1.3mmol)

was added having added triethylamine 0.19ml (1.3mmol) to the THF (5ml) solution of 0.25g (1.0mmol) of compounds obtained at the process (2-3), and maintaining -10--20 degree C at it, and it stirred for 30 minutes. 0.35g [ of bottom hydroxylamine hydrochlorides of ice-cooling ] (5.0mmol) and triethylamine 0.70ml (5.0mmol) was added to the reaction mixture which became cloudy, and it stirred for two days at the room temperature. Chloroform extracted, after making it acidity with 1-N hydrochloric acid. After saturation brine washed the organic layer, 0.10g (37.4% of yield) of 3-benzoylcinnamohydrozamic acid was obtained as a white crystal by a silica gel column chromatography's (methanol's: chloroform's :s acetic-acid =s 15:1:0.'s1) refining desiccation and the residue obtained by carrying out solvent distilling off, and crystalizing with ethyl-acetate-ethyl ether further.

mp.157-159 degree-C(dec.) 1 H-NMR(270MHz, DMSO-d6) deltappm:6.55 (1H, d, J= 15.4Hz), 7.51-7.93 (10H, m), 9.26 (1H, br.s), 10.71(1H, br.s).IR(KBr) cm-1:3459, 3298, 1670, 1648, 1625, 1521, 1431, 1296 and 1058, 978. [0069] Example 3 Composition of 4-[4-(N and N-dimethyl) amino]benzoylcinnamohydrozamic acid (Table -1: compound number 10) (3-1) It is pyridinium to a 4-BUROMO benzaldehyde 25.0g (135.1mmol) toluene (100ml) solution. 2.5g (10mmol) of p-toluene sulfonate was added, ethylene glycol 10.06g (162.1mmol) was added further, and heating reflux was carried out for 4 hours, removing the water generated by Dean Stark. After separating and removing the depositing solid-state after radiationnal cooling and distilling off a solvent, 2-(4-BUROMO phenyl)-1 and 3-dioxolane 25.83g (83.4% of yield) was obtained as a colorless oily liquid by distilling under reduced pressure.

bp.135-138 degree-C/1mmHg1 H-NMR(270MHz, CDCl3) deltappm:3.97-4.16 (4H, m), 5.77 (1H, s), 7.35 (2H, d, J= 8.1Hz), 7.51(2H, d, J= 8.1Hz). [0070] (3-2) Iodine was added to magnesium 0.95g (39mmol) THF (30ml) suspension one cup of micro spatula as an activator. The THF (10ml) solution of 7.02g (36mmol) of compounds obtained at the process (3-1) was added carefully, warming magnesium suspension. When foaming started on the way, after stopping heating and adding the remainder further, it stirred at the room temperature for 2 hours, and the dark-brown Grignard solution was prepared.

[0071] Thionyl chloride 5.35g (45mmol) was added to the toluene (100ml) suspension of 4.95g (30mmol) of 4-(N and N-dimethyl) aminobenzoic acids, and heating stirring was carried out at 100 degrees C for 2 hours. After distilling off a solvent, THF (100ml) and toluene (150ml) were added twice to the residue except superfluous thionyl chloride with azeotropy with toluene. After cooling this reaction mixture so that it may become -70--78 degree C, the Grignard reagent prepared previously was dropped adjusting so that an internal temperature may become -65--78 degree C. It ice-cooled, after stirring at -70--75 degree C for 1 hour, after dropping and, and the temperature up was carried out over 2 hours from under ice-cooling to the room temperature.

[0072] After suspending a reaction by the saturated ammonium chloride solution, it was made about one pH in the sulfuric-acid water solution 5%, and stirred at the room temperature for 1 hour. Ethyl acetate extracted, after making it alkalinity in a sodium-hydroxide water solution. Sodium bicarbonate water and saturation brine refined the organic layer, the silica gel column chromatography (chloroform: ethyl-acetate =10:1) refined desiccation and the residue obtained by carrying out solvent distilling off after washing, and 4-(N and N-dimethyl) amino benzoyl benzaldehyde 2.82g (37.1% of yield) was obtained as a yellow wax-like solid-state.

1 H-NMR(270MHz, CDCl3) deltappm:3.09 (6H, s), 6.68 (2H, d, J= 8.8Hz), 7.77 (2H, d, J= 9Hz), 7.83 (2H, d, J= 8.1Hz), 7.97 (2H, d, J= 8.1Hz), 10.11(1H, s). [0073] (3-3) Toluene (20ml) was made to suspend 1.01g [ of compounds ] (4.00mmol), and ethoxy carbonylmethyl (triphenyl) phosphine ylide 1.81g (5.2mmol) obtained at the process (3-2), and heating stirring was carried out at 80 degrees C under the nitrogen air current for 5 hours. It dilutes with ethyl acetate after radiationnal cooling, water and saturation brine refine after washing desiccation and the residue obtained by carrying out solvent distilling off with a silica gel column chromatography (chloroform: ethyl-acetate =10:1), and it is ethyl. 4-(N and N-dimethyl) amino benzoyl cinnamate 1.03g (79.6% of yield) was obtained as a yellow solid-state.

mp.130-131 degree-C1 H-NMR(270MHz, CDCl3) deltappm:1.35 (3H, t, J= 7.3Hz), 3.08 (6H, s), 4.28 (2H, q, J= 7.3Hz), 6.52 (1H, d, J= 15.1Hz), 6.68 (2H, d, J= 8.8Hz); 7.60 (2H, d, J= 8.1Hz), 7.70-7.80

(5H, m). [0074] (3-4) the methanol (20ml)-water (20ml) suspension of 0.97g (3.0mmol) of compounds obtained at the process (3-3) -- 0.19g (4.5mmol) of a lithium hydroxide and 1 hydrates -- adding -- 40 degrees C -- 9 hours -- warming -- it stirred. After making it acidity in 1-N hydrochloric-acid water solution, it extracted by the methyl ethyl ketone. Saturation brine washed the organic layer, methanol-diisopropyl ether washed desiccation after washing, and the solid-state obtained by carrying out solvent distilling off, and 0.62g (70% of yield) of 4-(N and N-dimethylamino) benzoyl cinnamic acid was obtained as a brown solid-state by drying.

mp.211-215 degree-C(dec.) 1 H-NMR(270MHz, DMSO-d6) deltappm:3.05 (6H, s), 6.66 (1H, d, J= 15Hz) 6.79 (2H, d, J= 8Hz), 7.63-7.69 (5H, m), 7.83(2H, d, J= 8Hz).IR(KBr) cm-1:3420, 2582(br), 1697, 1648, 1605, 1282, 986, 933, 773 [0075] (3-5) Having added triethylamine 0.093ml (0.66mmol) to the THF (3ml) suspension of 0.19g (0.64mmol) of compounds obtained at the process (3-4), and cooling by \*\*\*\* further, chloro carbonic acid isobutyl 0.086ml (0.66mmol) was added, and it stirred under ice-cooling for 15 minutes. After having added 0.23g (3.3mmol) of bottom hydroxylamine hydrochlorides of ice-cooling, adding triethylamine 0.46ml (3.3mmol) further and leaving it in a refrigerator below 4 degrees C overnight, it stirred for two days at the room temperature. After adding water and stopping a reaction, it extracted by the methyl ethyl ketone. Saturation brine refined the organic layer, the silica gel column chromatography (chloroform: methanol =10:1) refined desiccation and the residue obtained by carrying out solvent distilling off after washing, and 0.10g (48.8%) of 4-[4-(N and N-dimethyl) amino] benzoylcinnamohydrozamic acid was obtained as a light brown solid-state.

mp.amorphous solid.1 H-NMR(270MHz, DMSO-d6) deltappm:3.05 (6H, s), 6.58 (1H, d, J= 15Hz) 6.78 (2H, d, J= 8.8Hz), 7.54 (1H, d, J= 15Hz) 7.64-7.68 (6H, m), 9.11 (1H, br.s), 10.85(1H, br.s).IR(KBr) cm-1:3258(br), 1636, 1593, 1541, 1374, 1322, 1289, 1200, 1178 and 1147, 929. [0076] Oxalyl chloride 0.7ml (8.0mmol) was added to the dichloromethane (10ml) solution of 0.70g (3.12mmol) of synthetic 4-phenyl cinnamic acid of example 4 4-phenyl SHINNAMO hydroxamic acid (Table 1: compound number 19), and one drop of DMF was dropped further. After foaming stopped, it stirred at 40 degrees C for 1.5 hours. After having carried out azeotropy with toluene after carrying out reduced pressure distilling off of the solvent, and removing a superfluous oxalyl chloride, it dissolved in dichloromethane (10ml) again. Saturation sodium bicarbonate water (2ml) was added to the THF (5ml) suspension of 1.0g of hydroxylamine hydrochlorides (14.4mmol), and it was left for 10 minutes. After adding this THF layer to a previous dichloromethane solution at a stretch, it stirred violently for 1.5 hours.

[0077] After making it acidity in 1-N hydrochloric-acid water solution, it extracted by ethyl acetate (2 times) and the methyl ethyl ketone (1 time). After water and saturation brine washed all organic layers, 0.57g (76.3% of yield) of 4-phenyl SHINNAMO hydroxamic acid was obtained as a light brown crystal by crystallizing desiccation and the obtained residue which carried out solvent distilling off from chloroform.

mp.171-173 degree-C1 H-NMR(270MHz, DMSO-d6) deltappm:6.52 (1H, d, 15.1Hz), 7.3-7.8 (10H, m), 9.07 (1H, br.s), 10.79(1H, br.s).Anal.Calcd.C15H13NO2 0.1H2O C:74.18, H:5.56, N:5.77. Found C:74.22, H:5.50, N:5.68. [0078] Example 5 Composition of 3-{4-[N-(2-aminophenyl) amino] carbonyl} phenylpropiohydroxamic acid (Table 1: compound number 48) (5-1) Thionyl chloride 12.0ml (164mmol) was added to the toluene (100ml) suspension of 15.0g of terephthal aldehydic acid (100mmol), and heating stirring was carried out at 90 degrees C for 1.5 hours. After radiationnal cooling, after making the residue obtained by carrying out reduced pressure distilling off of a solvent and the superfluous thionyl chloride add and suspend dioxane (20ml), 2-nitroaniline 13.8g (100mmol) was added, and heating reflux was carried out for 6 hours. The solid-state which deposited by distilling off a solvent after separating the depositing solid-state after radiationnal cooling, and adding a methanol and an acetone to the obtained residue was separated, it dried, and N-(2-nitrophenyl)-4-formyl benzamide 15.41g (57.0% of yield) was obtained as a yellow solid-state.

1 H-NMR(270MHz, DMSO-d6) deltappm:7.43-7.49 (1H, m), 7.77-7.79 (2H, m), 8.03 (1H, d, J= 8.8Hz), 8.10 (2H, d, J= 8.8Hz) 8.15 (2H, d, J= 8.8Hz), 10.13 (1H, s), 10.96(1H, br.s).IR(KBr) cm-1:3357, 1706, 1672, 1607, 1588, 1508, 1341, 1277 and 1147, 855. [0079] (5-2) Ethoxy carbonylmethyl (triphenyl) phosphine ylide 2.51g (7.21mmol) was added to the toluene (25ml) suspension of 1.50g

(5.50mmol) of compounds obtained at the process (5-1), and heating stirring was carried out at 80 degrees C under the nitrogen air current for 9 hours. After radiation cooling, reaction mixture was diluted with ethyl acetate and after [ washing ] desiccation and a solvent were distilled off with water and saturation brine. A silica gel column chromatography (dichloromethane: ethyl-acetate =10:1) refines the obtained residue, and it is ethyl. 3-{4-[N-(2-nitrophenyl) amino] carbonyl phenyl} PUROENOETO 1.70g (90.0% of yield) was obtained as a yellow solid-state (cis--transformer 1:1 mixture). 1 H-NMR (270MHz, CDCl<sub>3</sub>) delappm:1.26 (3H, t, J= 3Hz), 1.36 (3H, t, J= 7.3Hz) 4.19 (2H, q, J= 7.3Hz), 4.30 (2H, q, J= 7.3Hz) 6.08 (1H, d, J= 12.5Hz), 6.55 (1H, d, J= 15.4Hz) 7.01 (1H, d, J= 12.5Hz), 7.2-7.3 (3H, m), 7.67-7.76 (6H, m), 7.97- 8.04 (4H, m) and 8.30 (2H, dd, J= 6.7, 1.5Hz) -- 9.01(2H, dd, J= 7.3, 1.5Hz).IR(KBr) cm-1:3374, 1716, 1684, 1640, 1606, 1583, 1498, 1432, 1337, 1254, 1177 and 1041, 849. [0080] (5-3) After suspending 0.70g (2.06mmol) of compounds obtained at the process (5-2) in a THF(25ml)-methanol (25ml), hydrogenation was performed by making palladium carbon (0.1g) into a catalyst 10%. It is ethyl by filtering a catalyst and washing with a methanol the residue obtained by distilling off a solvent after reaction termination. 3-{4-[N-(2-aminophenyl) amino] carbonyl phenyl} propanoate 0.46g (71.5% of yield) was obtained as a white solid-state.

mp.94-96 degree-C1 H-NMR(270MHz, DMSO-d6) delappm:1.17 (3H, t, J= 7.3Hz), 2.66 (2H, t, J= 7.3Hz) 2.93 (2H, t, J= 7.3Hz), 4.05 (2H, q, J= 7.3Hz) 4.87 (2H, br.s), 6.60 (1H, dd, J= 7.3, 8.1Hz) 6.79 (1H, d, J= 8.1Hz), 6.97 (1H, dd, J= 7.3, 8.1Hz) 7.17 (1H, d, J= 8.1Hz), 7.35 (2H, d, J= 8.1Hz) 7.91 (2H, d, J= 8.1Hz), 9.62(1H, s).IR(KBr) cm-1:3394, 3345, 1723, 1638, 1606, 1524, 1490, 1457, 1299 and 1185, and 746.Anal.Calcd.C18H20N2O3.0.1H<sub>2</sub>O C:68.81, H:6.48, N:8.91. Found C:69.21, H:6.45, N:8.97. [0081] (5-4) 0.4g [ of hydroxylamine hydrochlorides ] (5.75mmol) and sodium-ethoxide 0.4g (5.88mmol) was added to the ethanol (10ml) suspension of 0.20g (0.64mmol) of compounds obtained at the process (5-3), and heating reflux was carried out for 5 hours. After adding water and dissolving, saturation brine was added and it extracted by ethyl acetate and the methyl ethyl ketone. By carrying out after [ desiccation ] solvent distilling off of the organic layer, 0.11g (54% of yield) of 3-{4-[N-(2-aminophenyl) aminocarbonyl] phenyl} propionic hydroxamic acid was obtained as a light brown solid-state.

mp.amorphous solid1 H-NMR(270MHz, DMSO-d6) delappm:2.32 (2H, t, J= 7.3Hz), 2.89 (2H, t, J= 7.3Hz) 4.90 (2H, s), 6.60 (1H, dd, J= 7.3, 7.3Hz) 6.78 (1H, d, J= 6.6Hz), 6.96 (1H, dd, J= 7.3, 7.3Hz) 7.16 (1H, d, J= 8.1), 7.33 (2H, d, J= 8.1Hz), 7.91 (2H, d, J= 8.1Hz), 9.66 (1H, s), 10.23 (1H, s), 10.47 (1H, br.s). [0082] Example 1 of a pharmacological test It is known that the rise of the differentiation-inducing operation trial alkaline phosphatase (ALP) activity over Homo sapiens ovarian cancer origin A2780 cell will be known as an index of differentiation of a Homo sapiens colon cancer cell, for example, butanoic acid sodium will raise ALP activity (Young;Cancer Res., 45 and 2976 (1985), Morita;Cancer Res., and [42, 4540] (1982)). Then, the differentiation-inducing operation against an index by ALP activity was evaluated.

[0083] (The experiment approach) It wound 0.1ml of A2780 cells at a time so that it might become 96 hole plate with 15000 piece / well, and it added at a time 0.1ml of solutions of the test drug which carried out phase dilution in the culture medium on the next day. The TBS buffer solution (20mMTris, 137mM NaCl, pH7.6) washed the cell on a plate twice after culture for three days. Subsequently, 0.6mg/ml It added 0.05ml (9.6% diethanolamine, 0.5mM MgCl<sub>2</sub> (pH9.6)) of p-nitrophenylphosphate at a time, and incubated at the room temperature for 30 minutes. 3Ns After suspending a reaction by 0.05ml of NaOH solutions, the absorbance of 405nm was measured and it asked for the minimum concentration (ALPmin) of the drug with which the rise of ALP activity is caused.

(Experimental result) The example of representation of an experimental result was shown in Table -2 [Table 10].

[0084]

[Table 10]

Table-2: The differentiation-inducing operation sample offering compound to A2780 cell ALPmin (muM) ----- The compound of an example 1 The compound of one example 2 Compound of three examples.3 Compound of one example 4 Compound of 30 examples 5 10 butanoic-

acid sodium 10,000

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[Translation done.]